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Translation

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 24956 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP2002/014769	International filing date (*day/month/year*) 27 December 2002 (27.12.2002)	Priority date (*day/month/year*) 28 December 2001 (28.12.2001)
International Patent Classification (IPC) or national classification and IPC G01N 33/543, C12Q 1/68, G01N 33/552, 33/553, B01J 19/00		
Applicant FRAUNHOFER-GESELLSCHAFT ZUR FÖRDERUNG DER ANGEWANDTEN FORSCHUNG E.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16 May 2003 (16.05.2003)	02 August 2004 (02.08.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2002/014769

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-69, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-72, filed with the letter of 07 July 2004 (07.07.2004)

☒ the drawings:

pages 1/9-9/9, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-72	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-77	NO
Industrial applicability (IA)	Claims	1-72	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following documents:

D1: C. M. NIEMEYER et al., COLLOID POLYMER SCIENCE, Vol. 279, No. 1, January 2001 (2001-01), pages 68-72

D2: WO 01/73123 A (NANOSPHERE INC.) 4 October 2001 (2001-10-04)

D3: WO 01/23459 A (ARRAY BIOSCIENCE CORP.) 5 April 2001 (2001-04-05)

D4: WO 98/10289 A (BAKER BONNIE et al.) 12 March 1998 (1998-03-12)

D5: WO 01/18242 A (CZAKI ANDREA et al.) 15 March 2001 (2001-03-15)

2. **D1** discloses a microarray consisting of gold colloid particles derivatised with DNA oligonucleotides, said particles being bound to an aminopropyl-derivatised solid phase via complementary oligonucleotides. An analytical reaction takes place using oligonucleotide probes marked with fluorescence (see the specific passages of the document cited in the international search report).

As shown in particular by figure 13B and the

specific passages cited in the international search report, **D2** describes a method for detecting nucleic acid molecules, using, for example, nanoparticles immobilised on solid phase supports, bonding to the solid phase occurring by way of complementary oligonucleotides.

Neither of the above prior art publications, however, discloses the "directed" bonding of biomolecules, or the connecting layer between the support surface and the microstructure.

2.1. **D3** discloses multiplex-capable surface sensors for the SERS method, consisting of receptor-derivatised nanoparticles which are immobilised on quartz surfaces using, for example, a lithography method (see, in particular, figures 6a to 6b, 8b and 11f and the specific passages of the document cited in the international search report).

Although said prior art publication describes "directed" bonding of biomolecules, it does not describe the use of a connecting layer between the support surface and the microstructure.

- **D4** describes a biosensor based on derivatised solid phase supports, to which gold and silver nanoparticles are bound. Alternatively, bonding to the solid phase occurs by way of biotin or streptavidin (see figures 1A to 1D and the specific passages of the document cited in the international search report).

Although that prior art publication describes the use of a connecting layer between the support

surface and the microstructure, it does not describe the "directed" bonding of biomolecules.

3. Consequently, the functional element in claims 1 to 41, the production thereof as per claims 42 to 60 and the use thereof as per claims 61 to 72 is novel (PCT Article 33(2)).

4. **D4** is considered the closest prior art and differs from the functional element claimed in claim 1 only in that it does not indicate any suitable measure for achieving "directed" bonding of biomolecules (the nanoparticles as per **D4** adsorb only proteins).

The problem of interest therefore consists in replacing the non-specific adsorption of target molecules by nanoparticles by a technical measure that allows the nanoparticles to be covered with biomolecules in a reproducible, controlled manner, without the biological activity of the biomolecules being impaired. According to page 25 of the present description, this represents the desired "directed" bonding of the biomolecules.

4.1. The proposed solution consists in the derivatisation of the nanoparticles with first functional groups, which bond in a complementary manner to second functional groups on the biomolecules.

4.2. This type of measure is proposed in **D3**: in D3 nanoparticles immobilised on a substrate surface are derivatised with different receptors for later bonding to analyte molecules (corresponding to the biologically active molecules of the present application, for example oligonucleotides,

antibodies, DNA-bonding proteins, PNA; see **D3**, page 33, lines 15 to 26; page 35, lines 7 to 9; page 36, lines 2 to 4); this measure corresponds to the desired "directed" bonding of biomolecules as per the application.

In view of the lack of any other distinguishing technical indication for achieving a "directed" bonding of biomolecules, the use of the receptor-derivatised nanoparticles as per **D3** in a solid phase support as per **D4** appears obvious: claim 1 thus fails to meet the requirements of PCT Article 33(3).

5. Insofar as they are not also previously described in **D3** or **D4**, the embodiments detailed in the remaining claims concern common technical measures; consequently, an inventive step (PCT Article 33(3)) likewise cannot be acknowledged in respect of claims 2 to 72.